

(19) World Intellectual Property
Organization
International Bureau



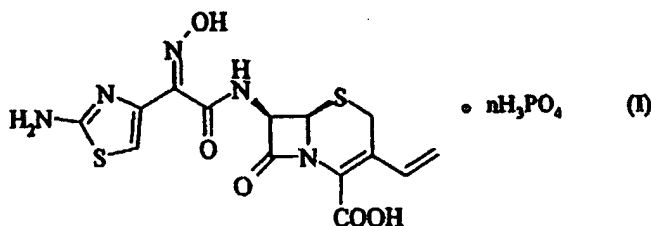
(43) International Publication Date
8 July 2004 (08.07.2004)

PCT

(10) International Publication Number
WO 2004/056835 A1

- (51) International Patent Classification⁷: C07D 501/22 (74) Agents: MINOJA, Fabrizio et al.; Via Rossini, 8, I-20122 Milano (IT).
- (21) International Application Number: PCT/EP2003/013524 (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (22) International Filing Date: 1 December 2003 (01.12.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
MI2002 A 002724
20 December 2002 (20.12.2002) IT
- (84) Designated States (*regional*): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- (71) Applicant (*for all designated States except US*): ANTIBIOTICOS S.P.A. [IT/IT]; Strada Rivoltana Km 6/7, I-20090 Rodano (MI) (IT).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): POZZI, Giovanni [IT/IT]; Via Belvedere, 19/F, I-20045 Besana Brianza (IT). MARTIN, Gomez, Patricio [ES/ES]; C/Juan Picornell, 28, 2^B, E-37006 Salamanca (ES). ALPEGIANI, Marco [IT/IT]; Via Tolmezzo, 12/5, I-20132 Milano (IT). CABRI, Walter [IT/IT]; Via Pisacane, 5, I-20089 Rozzano (IT).
- Published:
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: CRYSTALLINE CEFDINIR SALTS



(57) Abstract: Cefdinir crystalline salts of formula (I), in which n ranges from 1 to 3, the preparation and use thereof for the preparation and purification of cefdinir is herein disclosed. The salts of formula (I) can be obtained from cefdinir intermediates or crude cefdinir by treatment with phosphoric acid.

WO 2004/056835 A1

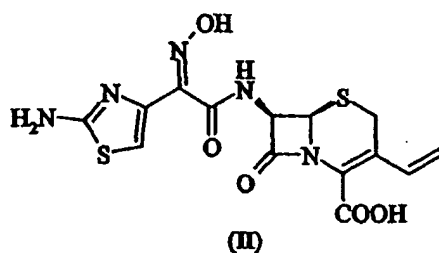
CRYSTALLINE CEFDINIR SALTS

Field of the invention

The present invention relates to crystalline cefdinir salts and to the process for the preparation thereof. These salts are useful intermediates in the synthesis and purification of cefdinir.

Background of the invention

Cefdinir (II),



whose chemical name is *[(-)-(6R,7R)]-7-[[(Z)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo [4.2.0] oct-2-en-2-carboxylic acid*, is a third generation semisynthetic cephalosporin for the oral use, characterized by a broad antibacterial activity spectrum and by antibiotic activity against gram-positive and gram-negative bacteria higher than that of other antibiotics for the oral administration. In particular, cefdinir shows an excellent antibacterial activity against staphylococci and streptococci.

Cefdinir is usually prepared through processes which envisage the protection of one or more of the primary amino, hydroxyimino or carboxy functions. The protective groups are removed at the end of the synthesis by means of acid hydrolysis.

US 4,559,334 discloses a method for the preparation of cefdinir benzhydryl ester, which is hydrolysed with TFA in anisole or with $\text{BF}_3 \cdot \text{Et}_2\text{O}$.

WO 01/79211 teaches to prepare cefdinir via protection of the

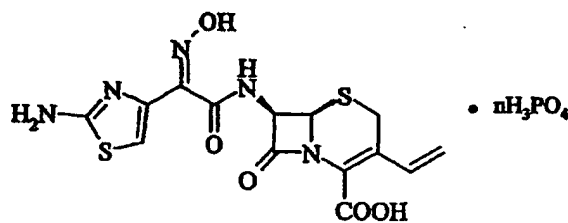
hydroxyimino and carboxy functions with a benzhydryl and a p-methoxybenzyl group respectively, which are subsequently removed with perchloric acid in an aprotic solvent and in the presence of an organic acid.

WO 97/24358 discloses the preparation of a cefdinir salt with p-toluenesulfonic acid wherein the hydroxyimino function is protected with a trityl group.

Since cefdinir is poorly stable to acids, the aforementioned methods give sometimes unsatisfactory yields and the purity does not comply with the pharmacopoeia standards. The resulting product must therefore be subjected to further purification, for example to recrystallization (according to US 4,935,507) or to formation of salts (according to US 6,350,869).

Detailed disclosure of the invention

It has now been found that cefdinir salts of formula (I)



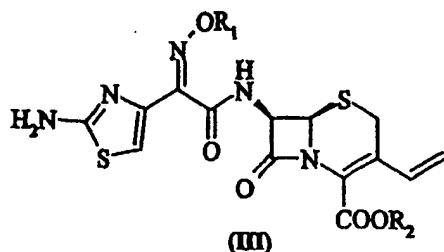
(I)

wherein n ranges from 1 to 3,

as well as hydrates and solvates thereof, allow to overcome the aforementioned drawbacks and are particularly useful intermediates in the preparation and purification of cefdinir.

Particularly preferred is the salt of formula (I) in which n is 2.

The salts of formula (I) are obtained by treating with phosphoric acid cefdinir protected forms of formula (III)



wherein

R_1 is a benzhydryl, trityl or p-methoxybenzyl group, and

R_2 is benzhydryl, t-butyl or p-methoxybenzyl group.

The reaction is carried out in a protic or aprotic, polar or apolar organic solvent, or in a mixture thereof. In more detail, the solvent is selected from nitriles, preferably acetonitrile or propionitrile; esters, preferably ethyl acetate, butyl acetate, ethyl formate and methyl acetate; amides, preferably N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), N-methylpyrrolidone (NMP); ketones, preferably acetone and methyl ethyl ketone; ethers, preferably tetrahydrofuran (THF) or dioxane; sulfoxides or sulfones, preferably dimethylsulfoxide (DMSO) and sulfolane; carboxylic acids, preferably formic and acetic acid; chlorinated solvents, preferably methylene chloride; and alcohols, preferably methanol, ethanol and isopropanol.

According to a particularly preferred embodiment of the invention, the solvent is acetonitrile.

Phosphoric acid is added, in the solid form or as an aqueous solution, in amounts ranging from 1 to 20 equivalents, preferably from 1 to 10 equivalents.

The reaction temperature ranges from -10°C to 60°C , more preferably from 0°C to 45°C .

The salts (I) usually crystallize in the reaction mixture and are recovered by filtration. To achieve complete precipitation, an organic solvent

selected from the following can be added: nitriles, preferably acetonitrile or propionitrile; esters, preferably ethyl acetate, butyl acetate, ethyl formate and methyl acetate; ketones, preferably acetone and methyl ethyl ketone; ethers, preferably diethyl ether, diisopropyl ether and tert-butylmethyl ether.

- 5 The preparation of the salts (I) allows to simultaneously hydrolyse the protective groups and obtain cefdinir intermediates which are easily recoverable in the crystalline form, stable and highly pure (the purity is generally higher than 98%).

10 The salts (I) can be easily converted to cefdinir, or to a hydrated or solvated form thereof, by means of conventional methods, for example by treatment with an organic base, preferably a tertiary amine, more preferably triethylamine, or with an inorganic base, preferably ammonia, or carbonates, bicarbonates, hydroxides or phosphates of alkaline metals, preferably sodium or potassium, and optional treatment of the resulting salts with conventional
15 acids. The reaction solvent can be water, or a mixture of water and alcohols, preferably methanol, ethanol, propanol or butanol; ketones, preferably acetone or methyl ethyl ketone, tetrahydrofuran or acetonitrile. The resulting solutions are treated with conventional acids; usually cefdinir precipitates as the solvate.

20 The salts of formula (I) are moreover particularly useful for the purification of crude cefdinir obtained by any other synthetic method. For this purpose, crude cefdinir is dissolved in water or in a protic or aprotic, polar organic solvent, or mixtures thereof, by addition of phosphoric acid, in the solid form or as an aqueous solution, in amounts ranging from 1 to 20 equivalents, preferably from 1 to 10 equivalents, at a temperature ranging
25 from -10°C to 60°C, preferably from 0 to 30°C. The organic solvent is selected from nitriles, preferably acetonitrile and propionitrile; amides, preferably N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA) and N-methylpyrrolidone (NMP); ketones, preferably acetone; ethers,

preferably tetrahydrofuran (THF); alcohols, preferably methyl, ethyl, propyl, isopropyl or *n*-butyl alcohol.

Usually, the salts (I) spontaneously crystallize from the reaction mixture, but crystallization can also be triggered and completed by addition of
5 an organic solvent selected from those previously indicated for this purpose.

Once precipitation is complete, the salts (I) are recovered and converted to cefdinir as described above.

The invention is now illustrated by means of the following examples.

EXAMPLES

10 Example 1

7-(Z)-[2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid phosphate

100 Grams of 7-(Z)-[2-(2-aminothiazol-4-yl)-2-trityloxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid dicyclohexylamine salt was dissolved in a
15 solution of 67 ml of 85% phosphoric acid in 1000 ml of acetonitrile. The mixture was heated at 45°C for 2 hours, until complete conversion of the starting product (HPLC). After cooling to 20°C, the precipitate was filtered and washed with acetonitrile. After drying, 61 grams of cefdinir phosphate was obtained.

20 HPLC purity = 98% (according to the method of the XIV Japanese pharmacopoeia)

¹H-NMR analysis confirmed the structure of the product, while ³¹P-NMR analysis confirmed the presence of phosphoric acid, which was also evident from the IR spectrum, showing characteristic bands at about 1115 and 970 cm⁻¹.

25 ¹H-NMR (DMSO-d₆, 300 MHz): 11.27 (1H, broad s), 9.47 (2H, d, *J*=8.3 Hz), 7.13 (2H, broad s), 6.93 (1H, dd, *J*=17.5 Hz and 11.5 Hz), 6.68 (1H, s), 5.80 (1H, dd, *J*=8.3 Hz and 5 Hz), 5.60 (1H, d, *J*=17.5 Hz), 5.33 (1H, d, *J*=11.5 Hz), 5.20 (1H, d, *J*=5 Hz); 3.80 and 3.57 (2H, AB system, *J*=17.9 Hz).

Example 2

7-(Z)-[2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid phosphate

80 Grams of 7-(Z)-[2-(2-aminothiazol-4-yl)-2-trityloxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid was dissolved in a solution of 60 ml of 85% phosphoric acid in 1000 ml of acetonitrile. The mixture was heated at 45°C for 2 hours until complete conversion of the starting product (HPLC). After cooling to 20°C, the product was filtered, washed with acetonitrile and dried. 61 Grams of cefdinir phosphate was obtained.

10 **Example 3**

7-(Z)-[2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid phosphate

10 Grams of 7-(Z)-[2-(2-aminothiazol-4-yl)-2-trityloxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid benzhydryl ester (prepared as reported in preparation A) is added to a solution of 21 ml of 85% phosphoric acid in 106 ml of acetonitrile. The mixture was heated at 45°C for 6 hours, until complete conversion of the starting product (HPLC). After cooling to 20°C, the precipitate was filtered, washed with acetonitrile and dried. 2.8 Grams of cefdinir phosphate was obtained.

20 HPLC purity = 99% (according to the method of the XIV Japanese pharmacopoeia).

Example 4

7-(Z)-[2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid phosphate

25 10 Grams of crude cefdinir (94% HPLC purity) (prepared according to WO 98/45299) was dissolved in 15 ml of 85% phosphoric acid and 15 ml of acetonitrile. The resulting solution was heated to 30°C and cefdinir phosphate was crystallized by addition of 230 ml of acetonitrile. After cooling to 20°C,

the precipitate was filtered, washed with acetonitrile and dried. 14 Grams of cefdinir phosphate was obtained.

HPLC purity ~ 99% (according to the method of the XIV Japanese pharmacopoeia).

5 Example 5

7-(Z)-[2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (cefdinir)

10 Grams of cefdinir phosphate was dissolved in 200 ml of water, adjusting the pH to 6 by addition of diluted ammonia at 5°C and the solution was treated with active charcoal. After removal of the charcoal, the pH was adjusted to 2.5 by addition of diluted hydrochloric acid at 35°C. After 15 minutes the solution was cooled to 5°C and the crystallized product was filtered, washed with water and dried. 6 Grams of cefdinir was obtained.

HPLC purity = 99.5% (according to the method of the XIV Japanese pharmacopoeia)

$T_{(1\%, 510\text{ nm})} = 99.0\%$ (test reported in US 4,935,507)

Preparation A

7-(Z)-[2-(2-Aminothiazol-4-yl)-2-trityloxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid benzhydryl ester

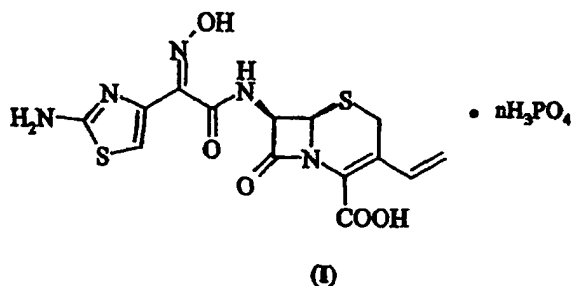
A suspension of 75 grams of 7-amino-3-vinyl-3-cephem-4-carboxylate benzhydryl hydrochloride in methylene chloride is treated under stirring with bis-trimethylsilylacetamide (90 ml) to obtain a clear solution. 60 Grams of 2-(Z)-(2-aminothiazol-4-yl)-2-trityloxyiminoacetic acid S-mercaptobenzothiazolyl ester is added and stirring is continued until completion of the reaction. The reaction mixture is poured in water (1 litre) and the phases are separated. The organic phase is dried over sodium sulfate and concentrated under vacuum. The residue is taken up with methylene chloride and methanol (1:1) under stirring. The solid is filtered and dried under vacuum to obtain about 105 g of

product.

¹H-NMR (CDCl₃, 300 MHz): 7.2-7.5 (26H, m), 7.05 (1H, dd, $J=17.6$ Hz and 11.3 Hz), 6.99 (1H, s), 6.74 (1H, d, $J=8.5$ Hz), 6.67 (2H), 5.95 (1H, dd, $J=8.5$ Hz e 5.0 Hz), 5.44 (1H, d, $J=17.9$ Hz), 5.30 (1H, d, $J=11.6$ Hz), 5.07
5 (1H, d, $J=5.0$ Hz), 3.41 e 3.42 (2H, AB system, $J_{AB}=17.6$ Hz).

CLAIMS

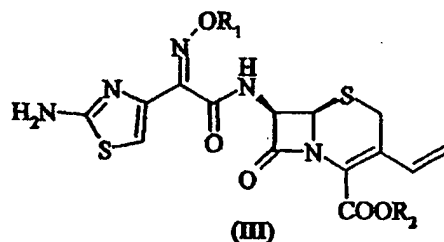
1. Cefdinir salts of formula (I)



wherein n ranges from 1 to 3,

the hydrates and solvates thereof.

2. Cefdinir salt as claimed in claim 1 wherein n is 2.
3. Cefdinir salts according to claim 1 or 2 in the crystalline form.
4. A process for the preparation of salts of formula (I) comprising the treatment with phosphoric acid of a compound of formula (III)



wherein

- R₁ is a benzhydryl, trityl or p-methoxybenzyl group, and
- R₂ is benzhydryl, t-butyl or p-methoxybenzyl group.

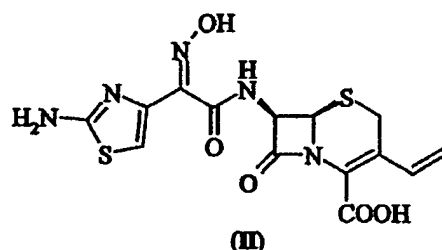
5. A process as claimed in claim 4 characterized in that use is made of an organic solvent selected from: acetonitrile, propionitrile, ethyl acetate, butyl acetate, ethyl formate, methyl acetate, N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), N-methylpyrrolidone (NMP), acetone, methyl ethyl ketone, tetrahydrofuran (THF), dioxane, dimethylsulfoxide

(DMSO), sulfolane, formic acid, acetic acid, methylene chloride, methanol, ethanol and isopropanol.

6. A process as claimed in claim 5 characterized in that the solvent is acetonitrile.

5 7. A process according to any one of claims 4 - 6 characterized in that use is made of 1 to 20 equivalents of phosphoric acid.

8. A process for the preparation of cefdinir (II)



10 comprising the treatment of salts of formula (I) with an organic or inorganic base, in which the organic base is triethylamine and the inorganic base is selected from ammonia, sodium carbonate or bicarbonate, potassium hydroxide or sodium or potassium phosphate, followed by treatment of the resulting solution with conventional acids.

15 9. A process according to claim 8 wherein the salt of formula (I) is obtained by reacting crude cefdinir with phosphoric acid

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 03/13524

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D501/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 304 019 A (FUJISAWA PHARMACEUTICAL CO) 22 February 1989 (1989-02-22) page 6, page 7 especially formula (I) and lines 37-51; pages 15-16, ref. 4 and claims	1,3-6,8
Y	WO 02 098884 A (CHANG YOUNG KIL ;KIM CHEOL KYUNG (KR); KIM HONG SUN (KR); LEE GWAN) 12 December 2002 (2002-12-12) claims; examples	1,3-6,8
A	GB 1 392 536 A (BRISTOL MYERS CO) 30 April 1975 (1975-04-30) claims 1,6,8	1-9
	-/-	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

A document member of the same patent family

Date of the actual completion of the international search

29 March 2004

Date of mailing of the international search report

22/04/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Chouly, J

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 03/13524

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2004 016623 A (SANDOZ AG ;WOLF SIEGFRIED (AT); KREMMINGER PETER (AT); LUDESCHER J) 26 February 2004 (2004-02-26) the whole document, especially example 9 and table/ figure 1/1	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/13524

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0304019	A	22-02-1989	AT 123221 T AU 617347 B2 CA 1297096 C DE 3853901 D1 DE 3853901 T2 EP 0304019 A2 ES 2072856 T3 HK 18496 A IE 67348 B1 JP 1250384 A JP 1943842 C JP 6074276 B KR 9708126 B1 MX 9203468 A1 US 4935507 A ZA 8805709 A	15-06-1995 28-11-1991 10-03-1992 06-07-1995 12-10-1995 22-02-1989 01-08-1995 09-02-1996 20-03-1996 05-10-1989 23-06-1995 21-09-1994 21-05-1997 01-09-1992 19-06-1990 26-04-1989
WO 02098884	A	12-12-2002	KR 2002092612 A EP 1392703 A1 WO 02098884 A1	12-12-2002 03-03-2004 12-12-2002
GB 1392536	A	30-04-1975	CA 988511 A1 DE 2222434 A1 DK 138458 B FR 2137586 A5 HU 163486 B JP 51014489 B NL 7205644 A SE 390171 B US 3757014 A	04-05-1976 23-11-1972 11-09-1978 29-12-1972 27-09-1973 10-05-1976 09-11-1972 06-12-1976 04-09-1973
WO 2004016623	A	26-02-2004	WO 2004016623 A1	26-02-2004